Emerging Trends in Acute Liver Failure in the United States

William M. Lee, MD
University of Texas Southwestern

Slide Presentation

Abstract: Acute liver failure (ALF) is a rare condition in which a variety of agents cause severe and sudden liver cell dysfunction. Sometimes termed fulminant hepatic failure, ALF is thought to affect about 2,000 in the U.S. per year. This overwhelming catastrophe leads to coma, multi-organ dysfunction, and death, primarily affecting young and previously healthy people. Over the past 30 years, the most frequent causes of ALF worldwide have been viral hepatitis, and drug-induced liver injury, with smaller numbers of cases due to a variety of etiologies. Until recently, little data have been available on ALF in the United States, the relative rarity of cases and lower population density in the U.S. limiting clinical studies. The ALF Study Group was formed in 1997 as a consortium of centers with experience in ALF from around the United States. The current report describes in detail the demographic profile, clinical features and outcome of patients developing ALF in the U.S. between 1998 and 2000, based on data collected prospectively by the ALF Study Group. Between January 1998 and October 2000, 258 patients were enrolled from 17 academic liver units around the United States. To be admitted to the study, patients met standard entry criteria for acute liver failure, i.e., coagulopathy (PT > 15 seconds or INR 1.5) and hepatic encephalopathy within 8 weeks of the first symptoms or jaundice without previous underlying liver disease.

Of the 258 patients, 190 (74%) were female. The reasons for the preponderance of women in this series have not been elucidated, as the underlying etiologies encountered do not share a female preponderance. Whether genetic or hormonal differences are important has not been explored. The impact of drug hepatotoxicity is exemplified by the finding that ALF due to acetaminophen or due to idiosyncratic drug reactions accounted for 52% of the total. Acetaminophen (ACM) poisoning was the most common cause of ALF, accounting for 98 (38%) cases. Although 79% of the ACM group were women, similar percentages were seen for the idiosyncratic drug reactions (74%) and for other causes of ALF. A dose-related toxin, acetaminophen is the single most common etiology for ALF in the U.S., Europe and Australia, although acetaminophen is rarely implicated in Asia. Only 12% of acetaminophen-related hospital admissions reach the threshold of developing symptoms of ALF, suggesting that the 98 cases observed in this study represent only a small fraction of the acetaminophen burden. The proportion of accidental cases in the present series was 60%% while 38% were thought to be overt suicidal ingestions. Accidental toxicity due to acetaminophen occurs when patients consume large amounts of drug over several days seeking pain relief, without realizing its possible harmful effects. Acetaminophen intoxication represents an acute event limited to a single-time-point ingestion or to a brief interval of exposure. As a result, ALT levels are extraordinarily high, bilirubin levels low and evidence of acute renal insufficiency and acidosis characterize the most severe cases, whose severity in terms of coma grade on admission equals that of other forms of ALF. Remarkably, these patients have a high spontaneous survival, perhaps attributable to the brevity of their drug exposure. Idiosyncratic drug reactions were responsible for another 35 (14%) cases, and included cases of troglitazone (4), bromfenac (4) and isoniazid (5). By comparison with the ACM cases, idiosyncratic reactions are characterized by slower onset, lower ALT, higher bilirubin levels, normal renal function but much poorer spontaneous survival. Hepatitis A and B caused 11 (4%) and 21 (8%) cases respectively. Seventy-three (28%) patients underwent hepatic transplantation, 61 of whom survived (84%

short-term survival). One hundred and twelve (43%) patients survived without transplantation (spontaneous survivors). Seventy-three (28%) patients died without transplantation. Overall survival in the group was 67%. Only 6% of acetaminophen patients were transplanted, 69% surviving spontaneously, while 25 died without receiving a liver graft. By contrast, 54% of the idiosyncratic group received a transplant, 20% died and 26% recovered spontaneously.

Drug-induced liver injury leading to acute liver failure accounts for 52% of all acute liver failure in the U.S. and is a disease of the developed world, since virtually no cases are found in developing countries. As such, developed nations should be able to institute preventive measures for this newly evolving crisis. With regard to acetaminophen, limitation of package size and better patient and physician education might help alleviate this burgeoning health problem.

Liver Toxicity

About CDER

Drug Information

Regulatory Guidance

CDER Conference

Specific Audiences

CDER Archives

Drug-Induced Liver Toxicity

Serious harm to the liver caused by drugs, and by the combination of drugs and substances is an important public health problem. As Americans ingest combin of prescription and over-the-counter drugs, herbal remedies, dietary supplement alcohol, the possibilities for harm and liver injury increases. Many of these pro are chemicals that are processed and detoxified by the liver. These chemical proc may produce substances that injure liver cells in some people and result in im liver functioning.

Although such adverse reactions are uncommon, they may be very serious and the sudden onset of liver failure or even death. Among patients with acute failure evaluated at liver transplantation centers in the United States, ingesti drugs has become the leading cause for liver failure, exceeding all other c combined. Serious drug-induced liver injury is also the leading single caus withdrawal of drugs from the market.

This web site includes the study documents, program, and presentations made conference "Drug-Induced Liver Disease: A National and Global Problem", February 12-13, 2001, in Chantilly VA. The conference was co-sponsored b Food and Drug Administration (FDA), the Pharmaceutical Research Manufacturers of America (PhRMA), and academic consultants in liver di represented by the American Association for the Study of Liver Diseases (AASL

Organizing and presenting this conference was not intended as an end in itself. I meant to initiate in the public arena continuing cooperative efforts to identif define the issues, to develop and agree upon research agendas, and to ed physicians and patients. Future postings at this web page includes presenting r of the workshop discussion groups, and proposing research and educational w be done.

We encourage you to contribute your ideas about this topic. Please send comments to seniorj@cder.fda.gov.

Drug-Induced Liver Injury: A National and Global Problem
12-13 February 2001, Westfields Conference Center, Chantilly VA

Final Program

White Papers (Pre-Conference Study Documents)

- **Pre-Clinical: Nonclinical Assessment of Potential Hepatotoxicity in**
- **Clinical**
- **Postmarketing Considerations**

Invited Presentations

Monday, February 12, 2001

Opening talks - Overview

- Welcome, Program Structure, Goals of the Conference and Workshop
  John Senior, MD, Food & Drug Administration (FDA)
- Drug-Induced Liver Injury Impacts on the Food and Drug Administration (FDA)
  Robert Temple, M.D., Associate Director for Medical Policy
  Center for Drug Evaluation and Research, FDA
- Impact of Hepatotoxicity on the Pharmaceutical Industry
  Bert Spilker, Ph.D., M.D., Senior Vice President, PhRMA, Washington, D.C.
- Impact of Drug-Induced Liver Injury on Hepatology and the Practice of Medicine
  William M. Lee, MD, Professor of Medicine, University of Texas Southwestern Medical Center

State-of-the-Art Presentations

- Pre-Clinical Issues in Drug Development
  François Ballet M.D., Ph.D., Aventis, Paris
- Clinical Picture and Issues in the Clinical Phases of Drug Development
  Neil Kaplowitz, M.D., University of Southern California, Los Angeles
- Post-Marketing: State of the Art and Issues Defined
  Peter K Honig, MD, MPH, Director, Office of Postmarketing Drug Risk Assesment, FDA

Tuesday, February 13, 2001

Current Topics in Hepatology

- How are these problems being addressed in Europe?
  Roger Williams, Professor of Hepatology, Institute of Hepatology, University College, London
- Looking for hepatotoxicity, working up patients, and assessing causality
  James W. Freston, M.D., Ph.D., University of Connecticut Health Center, Farmington, CT
- Emerging Trends in Acute Liver Failure in the United States
  William M. Lee, MD, University of Texas Southwestern Medical Center
- Pharmacogenomics: Dangerous drug or susceptible patient?
  Paul B. Watkins, M.D., University of North Carolina at Chapel Hill, NC

Back to Top Back to Drug Info